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(54) Title: PHENYLACETAMIDO- PYRAZOLE DERIVATIVES AND THEIR USE AS ANTITUMOR AGENTS

(57) Abstract: Phenylacetamido-pyrazoles of Formula (I) and, more particularly, N-(5-cycloalkyl-1H-pyrazol-3-yl) phenylacetamido derivatives, optionally further substituted as reported in the description; or pharmaceutically acceptable salts thereof; are useful in the treatment of cell proliferative disorders, e.g.cancer, associated with an altered cell cycle dependent kinase activity. Formula (I).



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activation of cyclin A/cdc2 (cdk1) and cyclin B/cdc2 are required for the onset of metaphases. For a general reference to cyclins and cyclin-dependent kinases see, for instance, Kevin R. Webster et al, in Exp. Opin. Invest. Drugs, 1998, Vol. 7(6), 865-887. Checkpoint controls are defective in tumor cells due, in part, to dysregulation of cdk activity. For example, altered expression of cyclin E and cdk2 has been observed in tumor cells, and deletion of the cdk inhibitor p27 KIP gene in mice has been shown to result in a higher incidence of cancer.

Increasing evidence supports the idea that the cdk2s are rate-limiting enzymes in cell cycle progression and, as such, represent molecular targets for therapeutic intervention.

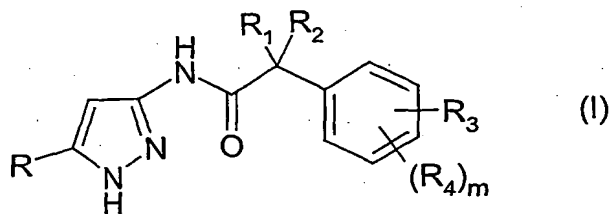
In particular, the direct inhibition of cdk/cyclin kinase activity should be helpful in restricting the unregulated proliferation of a tumor cell.

SUMMARY OF THE INVENTION

It is an object of the invention to provide compounds which are useful in treating cell proliferative disorders caused by and/or associated with an altered cell cycle dependent kinase activity. It is another object to provide compounds which have cdk/cyclin kinase inhibitory activity.

The present inventors have now discovered that certain phenylacetamido-pyrazoles are endowed with cdk/cyclin kinase inhibitory activity and are thus useful in therapy as antitumor agents and lack, in terms of both toxicity and side effects, the aforementioned drawbacks associated with currently available antitumor drugs.

More specifically, the phenylacetamido-pyrazoles of the invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and



wherein

R is an optionally substituted C₃-C₅ cycloalkyl group;

R₁ and R₂, the same or different, represent hydrogen, halogen, amino, hydroxy or a group selected from straight or branched C₁-C₅ alkyl optionally substituted by amino or hydroxy, straight or branched C₁-C₅ perfluorinated alkyl or straight or branched C₁-C₅ alkoxy or, taken together with the carbon atom to which they are bonded, R₁ and R₂ form an exomethylene (>C=CH₂) group or a C₃-C₄ cycloalkyl group;

R₃, in position 3 or 4 of the phenyl ring, is a group of formula



representing a 5 or 6 membered saturated or unsaturated nitrogen containing heterocycle; optionally containing from 1 to 2 additional heteroatoms, the same or different, selected from nitrogen, oxygen or sulfur; optionally substituted in any of the free positions by one or more groups selected from halogen; hydroxy; aminocarbonyl; C₁-C₄ alkylaminocarbonyl; oxo groups (>C=O, >S=O, >SO₂); exomethylene (>C=CH₂); straight or branched C₁-C₄ alkyl, perfluorinated alkyl, hydroxyalkyl or alkoxy groups; C₂-C₄ alkenyl or aryl groups; optionally condensed with carbocyclic or heterocyclic rings, either saturated or unsaturated, either monocyclic or bicyclic, each of which being optionally further substituted as above defined;

m is 0 or an integer from 1 to 4;

if present, each R₄ is, the same or different, halogen, hydroxy or a group selected from straight or branched C₁-C₄ alkyl, perfluorinated alkyl or alkoxy; or a pharmaceutically acceptable salt thereof;

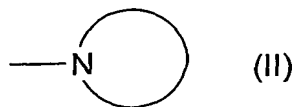
provided that:

- a) when R is cyclopropyl and R₁ and R₂ are both hydrogen atoms, then the nitrogen containing heterocycle of formula (II) is other than 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl or 1,2,3-triazol-1-yl; and

R is an optionally substituted C₃-C₅ cycloalkyl group;

R₁ and R₂, the same or different, represent hydrogen, halogen, amino, hydroxy or a group selected from straight or branched C₁-C₅ alkyl optionally substituted by amino or hydroxy, straight or branched C₁-C₅ perfluorinated alkyl or straight or branched C₁-C₅ alkoxy or, taken together with the carbon atom to which they are bonded, R₁ and R₂ form an exomethylene (>C=CH₂) group or a C₃-C₄ cycloalkyl group;

R₃, in position 3 or 4 of the phenyl ring, is a group of formula



representing a 5 or 6 membered saturated or unsaturated nitrogen containing heterocycle; optionally containing from 1 to 2 additional heteroatoms, the same or different, selected from nitrogen, oxygen or sulfur; optionally substituted in any of the free positions by one or more groups selected from halogen; hydroxy; aminocarbonyl; C₁-C₄ alkylaminocarbonyl; oxo groups (>C=O, >S=O, >SO₂); exomethylene (>C=CH₂); straight or branched C₁-C₄ alkyl, perfluorinated alkyl, hydroxyalkyl or alkoxy groups; C₂-C₄ alkenyl or aryl groups; optionally condensed with carbocyclic or heterocyclic rings, either saturated or unsaturated, either monocyclic or bicyclic, each of which being optionally further substituted as above defined;

m is 0 or an integer from 1 to 4;

if present, each R₄ is, the same or different, halogen, hydroxy or a group selected from straight or branched C₁-C₄ alkyl, perfluorinated alkyl or alkoxy; or a pharmaceutically acceptable salt thereof;

provided that:

- a) when R is cyclopropyl and R₁ and R₂ are both hydrogen atoms, then the nitrogen containing heterocycle of formula (II) is other than 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl or 1,2,3-triazol-1-yl; and
- b) when R is cyclopropyl, one of R₁ and R₂ is a hydrogen atom and the other is methyl, ethyl, n-propyl or n-butyl, then the nitrogen-containing heterocycle of formula (II) is other than 1,3-dihydro-2H-isoindol-2-yl or 1-oxo-1,3-dihydro-2H-isoindol-2-yl.

Accordingly, in the present invention and unless otherwise specified, where only one tautomer is indicated for the compounds of formula (I), the other is also within the scope of the present invention.

5 The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers which are all within the scope of the present invention.

Just as an example, the compounds of formula (I) wherein R_1 is alkyl, for instance methyl, and R_2 is hydrogen, have an asymmetric carbon atom and, hence, both the (R) and (S) optical isomers as well as the racemic (R,S) admixture are within the scope of
10 the invention.

Likewise, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

15

As used herein, unless otherwise specified, the term C_3 - C_5 cycloalkyl comprises cyclopropyl, cyclobutyl and cyclopentyl.

With the term halogen atom, unless otherwise indicated, we intend iodine, bromine, chlorine or fluorine.

20

As used herein, unless otherwise indicated, the terms straight or branched C_1 - C_5 alkyl or alkoxy groups include, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

25

With the term straight or branched perfluorinated C_1 - C_5 alkyl group we intend any of the above alkyl groups which are substituted by more than one fluorine atom such as, for instance, trifluoromethyl, trifluoroethyl and the like.

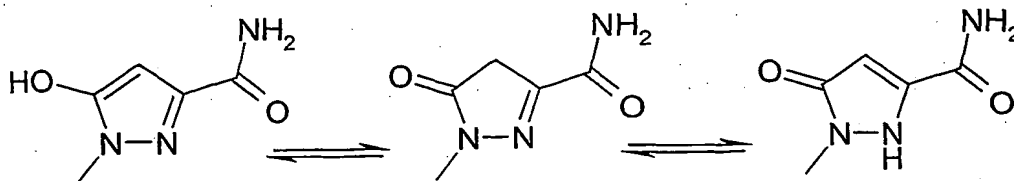
As used herein, unless otherwise indicated, the term C_2 - C_4 alkenyl includes, for instance, a group selected from vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and the like.

the like; one or two oxo groups may be also bonded to a sulphur atom so as to yield, for instance, thiazolidine-1,1-oxide, isothiazolidine-1,1-oxide and the like.

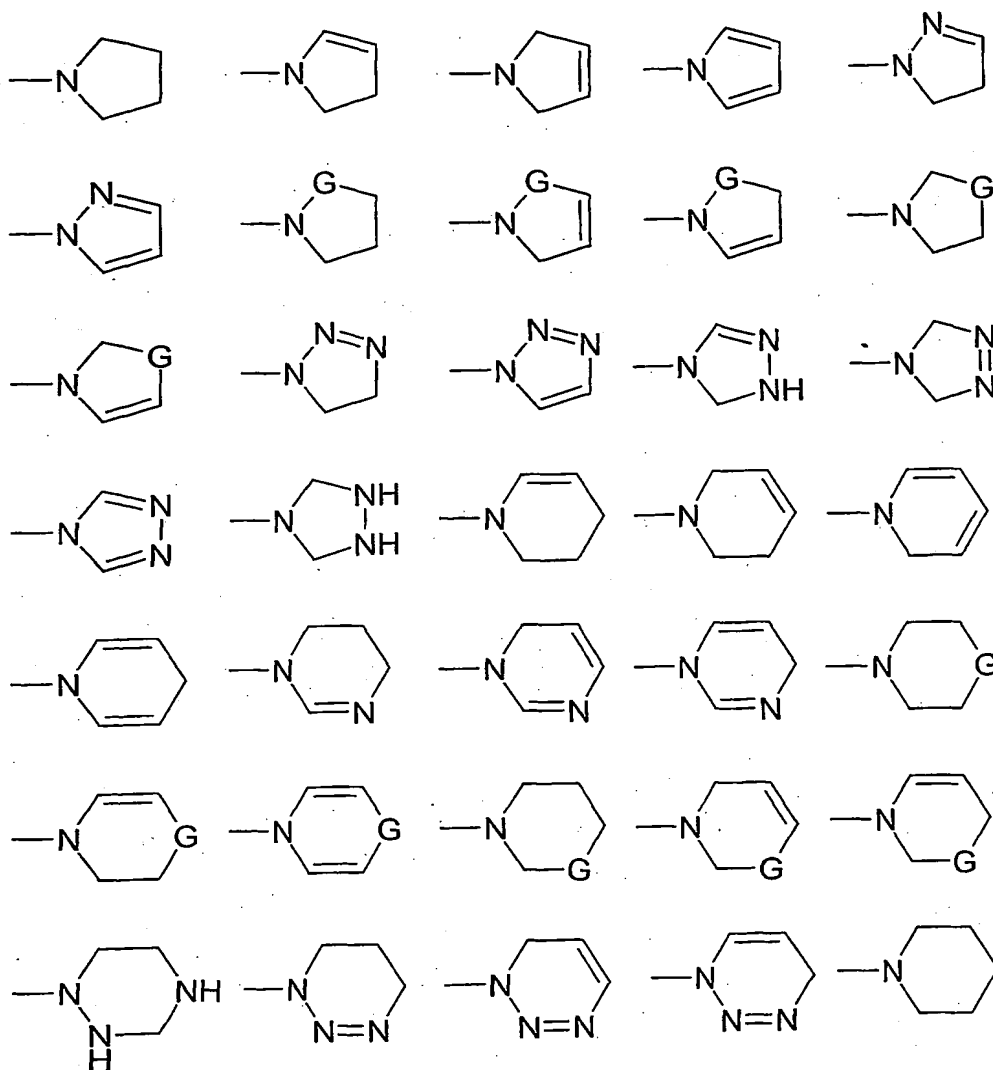
According to the above indicated substituents and unless otherwise specified, any of the above R or R₃ groups may be optionally substituted in any of the free positions by one or more groups independently selected from halogen, nitro, oxo groups, cyano, alkyl, perfluorinated alkyl, hydroxyalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, hydroxy, alkoxy, perfluorinated alkoxy, aryloxy, heterocyclyoxy, methylenedioxy, alkylcarbonyloxy, arylcarbonyloxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxy carbonyl, amino, ureido, alkylamino, dialkylamino, arylamino, diarylamino, formylamino, alkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, alkoxy carbonylamino, alkoxyimino, alkylsulfonylamino, arylsulfonylamino, formyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, heterocyclylcarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylthio and alkylthio.

Unless otherwise indicated, any of the terms such as, for instance, alkylthio, alkylamino, dialkylamino, alkoxy carbonyl, alkoxy carbonylamino, heterocyclylcarbonyl, heterocyclylcarbonylamino, cycloalkyloxy carbonyl and the like, include groups wherein the alkyl, alkoxy, aryl, cycloalkyl and heterocyclyl moieties are as above defined.

When referring to the compounds of formula (I) wherein the nitrogen-containing heterocycle of formula (II) may give rise to equivalent tautomeric form, for instance as reported below



it is clear to the man skilled in the art that all of the said forms are to be intended as within the scope of the present invention.



wherein G represents a group -NH-, -O-, -S- or -SO₂-.

Still more preferred are the compounds of formula (I) wherein R, R₁, R₂, R₄ and m are
 5 as above defined and R₃ is a group selected from: 1-pyrrolidinyl; 2-oxo-1-pyrrolidinyl;
 3-methyl-2-oxo-1-pyrrolidinyl; 2-methyl-5-oxo-1-pyrrolidinyl; 2-ethyl-5-oxo-1-
 pyrrolidinyl; 2-oxo-5-phenyl-1-pyrrolidinyl; 2-oxo-1,3-oxazolidin-3-yl; 2-oxo-
 3,3a,6,6a-tetrahydrocyclopenta-[b]pyrrol-1(2H)-yl; 2-(hydroxymethyl)-5-oxo-1-
 pyrrolidinyl; 3-hydroxy-2-oxo-1-pyrrolidinyl; 4-hydroxy-2-oxo-1-pyrrolidinyl; 3-
 10 hydroxy-4,4-dimethyl-2-oxo-1-pyrrolidinyl; 2-oxo-3-pyrrolidinecarboxamide; 5-oxo-3-
 pyrrolidinecarboxamide; 5-oxo-2-pyrrolidinecarboxamide; 1,3-dioxo-1,3-dihydro-2H-
 isoindol-2-yl; 1-hydroxy-3-oxo-1,3-dihydro-2H-isoindol-2-yl; 1-oxooctahydro-2H-

Examples of preferred compounds of the invention of formula (I), also comprehensive of the above derivatives of formula (I'), optionally in the form of pharmaceutically acceptable salts, include:

1. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
2. (2R)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
3. (2S)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
4. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]acetamide;
5. N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
6. (2R)-N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
7. (2S)-N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
8. N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]acetamide;
9. N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
10. (2R)-N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
11. (2S)-N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
12. N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]acetamide.
13. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
14. (2S)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;

30. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-5-phenyl-1-pyrrolidinyl)phenyl]acetamide;
31. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-5-phenyl-1-pyrrolidinyl)phenyl]propanamide;
- 5 32. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-3,3a,6,6a-tetrahydrocyclopenta[b]pyrrol-1(2H)-yl)phenyl]acetamide;
33. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-3,3a,6,6a-tetrahydrocyclopenta[b]pyrrol-1(2H)-yl)phenyl]propanamide;
34. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-{4-[2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]phenyl} acetamide;
- 10 35. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-{4-[2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]phenyl}propanamide;
36. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-hydroxy-2-oxo-1-pyrrolidinyl)phenyl]acetamide;
- 15 37. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-hydroxy-2-oxo-1-pyrrolidinyl)phenyl]propanamide;
38. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(4-hydroxy-2-oxo-1-pyrrolidinyl)phenyl]acetamide;
39. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(4-hydroxy-2-oxo-1-pyrrolidinyl)phenyl]propanamide;
- 20 40. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-hydroxy-4,4-dimethyl-2-oxo-1-pyrrolidinyl)phenyl]acetamide;
41. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-hydroxy-4,4-dimethyl-2-oxo-1-pyrrolidinyl)phenyl]propanamide;
- 25 42. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-2-oxo-3-pyrrolidinecarboxamide;
43. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-2-oxoethyl}phenyl)-2-oxo-3-pyrrolidinecarboxamide;
44. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-5-oxo-3-pyrrolidinecarboxamide;
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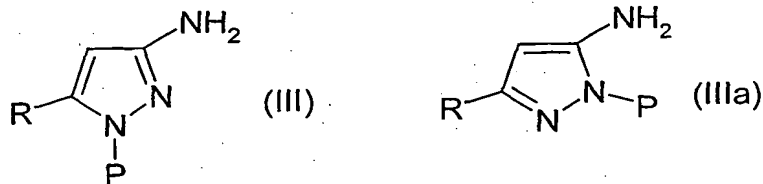
60. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]propanamide;
61. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-oxo-1H-benzo[de]isoquinolin-2(3H)-yl)phenyl]propanamide;
- 5 62. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1H-pyrrol-1-yl)phenyl]acetamide;
63. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1H-pyrrol-1-yl)phenyl]propanamide;
64. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(7-hydroxy-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)phenyl]acetamide;
65. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)phenyl]propanamide;
- 10 66. 2-[2-chloro-4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]-N-(5-cyclopropyl-1H-pyrazol-3-yl)acetamide;
67. 2-[2-chloro-4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]-N-(5-cyclopropyl-1H-pyrazol-3-yl)propanamide;
- 15 68. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxotetrahydro-1(2H)-pyrimidinyl)phenyl]acetamide;
69. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxotetrahydro-1(2H)-pyrimidinyl)phenyl]propanamide;
70. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-1,2,4-triazolidin-4-yl)phenyl]acetamide;
- 20 71. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-1,2,4-triazolidin-4-yl)phenyl]propanamide;
72. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-1-imidazolidinyl)phenyl]acetamide;
- 25 73. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-1-imidazolidinyl)phenyl]propanamide;
74. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxo-1-imidazolidinyl)phenyl]acetamide;
75. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxo-1-imidazolidinyl)phenyl]propanamide;
- 30

92. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-piperidiny)phenyl]acetamide;
 93. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-piperidiny)phenyl]propanamide;
 94. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-piperazinyl)phenyl]acetamide;
 95. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-piperazinyl)phenyl]propanamide;
 5 96. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(4-morpholinyl)phenyl]acetamide;
 97. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(4-morpholinyl)phenyl]propanamide;
 98. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-piperidiny)phenyl]acetamide;
 99. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-pyrrolidiny)phenyl]propanamide;
 100. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-piperidiny)phenyl]propanamide.

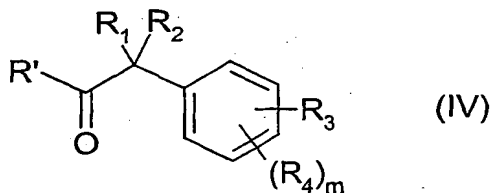
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As formerly indicated, a further object of the invention is represented by the process for preparing the compounds of formula (I), hence including also those of formula (I'). The compounds of formula (I) and the salts thereof, object of the present invention, may be thus obtained by a process comprising:

- 15 a) reacting the compounds of formula (III) or the regioisomers of formula (IIIa)



wherein R is as above defined and P represents a suitable nitrogen-pyrazole protecting group, with the compounds of formula (IV)



- 20 wherein R₁, R₂, R₃, R₄ and m have the above reported meanings and R' represents hydroxy or a halogen atom, thus obtaining the compounds of formula (V) or (Va)

triethylamine, N-methylmorpholine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as dichloromethane, chloroform, diethylether, tetrahydrofuran, 1,4-dioxane, acetonitrile, toluene or N,N-dimethylformamide, at a temperature ranging from about 0°C to reflux.

5

As far as the compounds of formula (III) or (IIIa) are concerned, suitable P groups are those conventionally used to protect pyrazole-nitrogen atoms. Preferably, for both compounds (III) and (IIIa), P represents a tert-butoxycarbonyl (boc) group.

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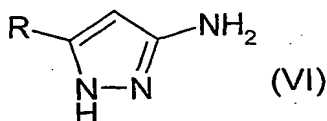
In step b) of the process, the compounds of formula (V) or (Va) are converted into the desired derivatives of formula (I) by deprotecting the pyrazole-nitrogen atom, according to conventional methods.

15

As an example, deprotection from "boc" may occur by acidic hydrolysis, for instance in the presence of trifluoroacetic, formic or sulphuric acid, in a suitable solvent such as dichloromethane, 1,4-dioxane or ethanol, at a temperature ranging from about 0°C to room temperature.

20

The compounds of formula (III) or (IIIa) are known or may be prepared according to known methods by starting from the corresponding deprotected derivatives of formula (VI)



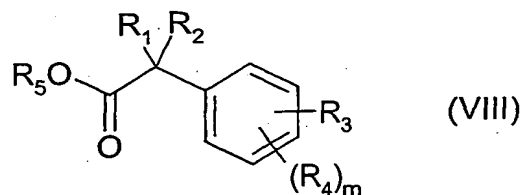
wherein R is as above defined.

For a reference to the preparation of the compounds of formula (III) see, for instance, the aforementioned US 6,218,418.

25

When preparing the compounds of formula (IIIa), the compounds of formula (VI) are protected, for instance as "boc" derivatives through reaction with tert-butoxycarbonylanhydride, in the presence of a dichloromethane/water admixture and of an inorganic base such as sodium hydroxide, carbonate or hydrogenocarbonate. This same reaction may be also carried out in dichloromethane, chloroform, toluene, tetrahydrofuran or 1,4-dioxane and in the presence of an organic base, for instance

30

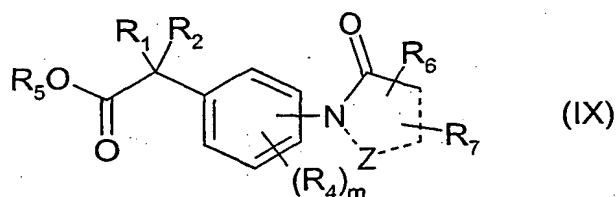


bearing the desired R_3 residue, followed by the acidic or basic hydrolysis of the ester group.

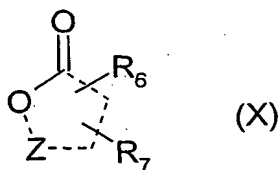
- The above hydrolysis to yield the compounds of formula (IV) can be carried out with a base such as sodium or potassium hydroxide, in a suitable solvent such as methanol or ethanol or, alternatively under acidic conditions, in the presence of hydrochloric, hydrobromic or sulphuric acid, in a suitable solvent such as acetic acid, tetrahydrofuran or 1,4-dioxane, at a temperature ranging from room temperature to reflux.

- 10 The compounds of formula (VIII) are known or can be prepared according to known methods.

- As an example, the compounds of formula (VIII) wherein R_3 is a pyrrolidine or piperidine ring, either saturated or unsaturated, as per formula (IX) below wherein the dotted lines represent a single or double bond, R_1 , R_2 , R_4 , R_5 and m are as above defined, Z is methylene, ethylene, $C=O$ or $CH-OH$, R_6 and R_7 are, each independently, hydrogen atoms or methyl, ethyl, phenyl, hydroxymethyl, hydroxy, aminocarbonyl or allyl groups or, taken together, may form a keto group ($=O$) or a fused aryl or cycloalkyl group optionally further substituted

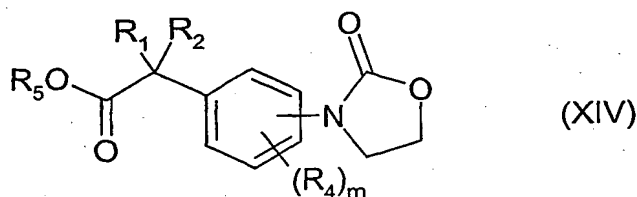


- 20 can be prepared by reacting the compounds of formula (VII) with the compounds of formula (X)



triphenylphosphine, in a suitable solvent such as dichloromethane, tetrahydrofuran or 1,4-dioxane, at a temperature ranging from room temperature to reflux.

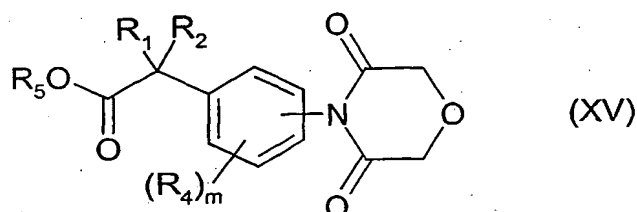
The compounds of formula (VIII) wherein R_3 is a 1,3-oxazolidin-2-one system, as per formula (XIV) below wherein R_1 , R_2 , R_4 , R_5 and m are as above defined



can be prepared by reacting the compounds of formula (VII) with 2-chloroethylchloroformate under Schotten-Bauman conditions.

More in particular, the reaction can be carried out in the presence of aqueous sodium hydroxide and toluene at room temperature, or with a conventional organic base under anhydrous conditions; the intermediate compound thus prepared, is then treated with an aqueous base, for instance sodium hydroxide or methoxide, in a suitable solvent such as water or water-methanol admixtures, at a temperature ranging from room temperature to about 60°C.

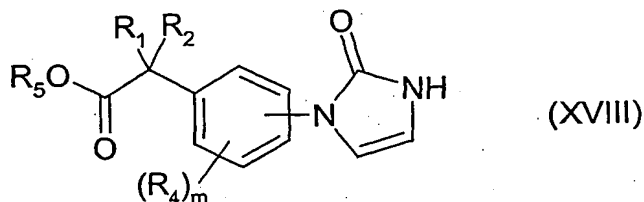
The compounds of formula (VIII) wherein R_3 is a 3,5-morpholinedione system, as per formula (XV) below wherein R_1 , R_2 , R_4 , R_5 and m are as above defined



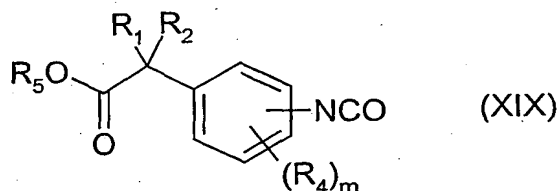
can be prepared by reacting the compounds of formula (VII) with diglycolic acid, in the presence of a suitable solvent, for instance water-tetrahydrofuran admixtures, at refluxing temperature.

The compounds of formula (VIII) wherein R_3 is a 2,4-dihydro-3H-1,2,4-triazol-3-one system, as per formula (XVI) below wherein R_1 , R_2 , R_4 , R_5 and m are as above defined

The compounds of formula (VIII) wherein R_3 is a 1,3-dihydro-2H-imidazol-2-one, as per formula (XVIII) wherein R_1 , R_2 , R_4 , R_5 and m are as above defined



can be prepared through a process comprising reacting the compounds of formula (VII) with a carbonyl equivalent that is, for instance, phosgene, diphosgene, triphosgene, carbonyldiimidazole or disuccinimidocarbonate, thus obtaining the compounds of formula (XIX) below

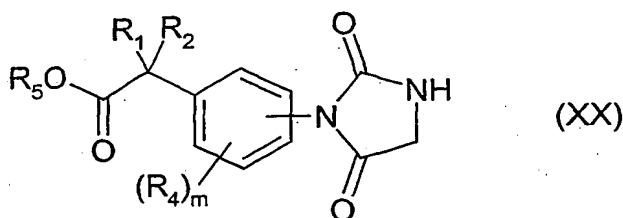


and by reacting the compounds of formula (XIX) with 2-aminoacetaldehyde dimethylacetale followed by acidic treatment.

The reaction of the compounds of formula (VII) with the carbonyl equivalent is carried out in a suitable solvent such as diethylether, tetrahydrofuran, 1,4-dioxane or N,N -dimethylformamide, at a temperature ranging from room temperature to about 80°C .

The subsequent reaction with 2-aminoacetaldehyde dimethylacetale can be carried out in a suitable solvent such as dichloromethane, chloroform, tetrahydrofuran or 1,4-dioxane, at room temperature, thus affording an intermediate compound which is directly treated with an acid, for instance a water:trifluoroacetic acid=1:1 admixture, at a temperature ranging from room temperature to reflux.

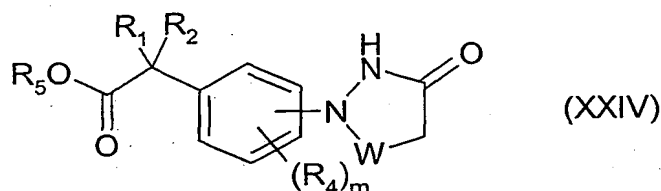
The compounds of formula (VIII) wherein R_3 is a 2,4-imidazolidindione system, as per formula (XX) wherein R_1 , R_2 , R_4 , R_5 and m are as above defined



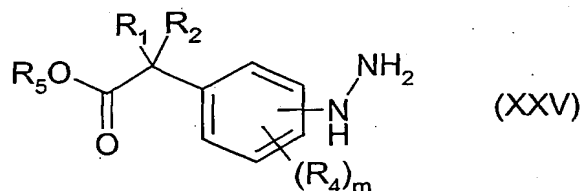
can be prepared by reacting the compounds of formula (VII) with ethyl (2E)-3-ethoxy-2-propenoylcarbamate, prepared as described in Journal of American Chemical Society 111, 374 (1989), in the presence of a suitable solvent such as 1-butanol and at refluxing temperature and, subsequently, by treatment with aqueous sodium hydroxide.

5

The compounds of formula (VIII) wherein R_3 is a 2,4-dihydro-3H-pyrazol-3-one or a 2,5-pyrazolidindione, as per formula (XXIV) below wherein R_1 , R_2 , R_4 , R_5 and m are as above defined and W is CH_2 or $C=O$



- 10 can be prepared by a process comprising reacting the compounds of formula (VII) with sodium nitrite in acidic medium and by treating the resulting diazonium salt with sodium sulphite or tin chloride, thus obtaining the compounds of formula (XXV)

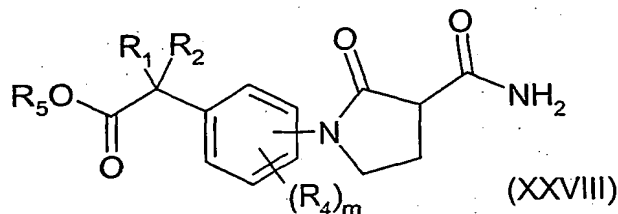


- 15 and by reacting the compounds of formula (XXV) with 3-chloropropionic acid or malonic acid, thus obtaining the compounds of formula (XXIV) wherein W is CH_2 or CO , respectively.

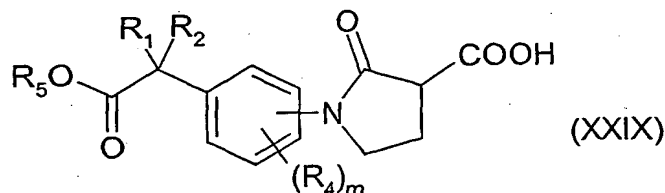
- The reaction of the compounds of formula (VII) with sodium nitrite is carried out in the presence of an acid, for instance aqueous hydrochloric acid, at about $0^\circ C$; the subsequent treatment with a reducing agent such as sodium sulphite in water or tin trichloride in aqueous hydrochloric acid, allows to obtain the compounds of formula (XXV).
- 20

- The reaction of the compounds of formula (XXV) with 3-chloropropionic acid, to yield the compounds of formula (XXIV) wherein W is CH_2 can be carried out without a solvent, at a temperature ranging from about $150^\circ C$ to about $210^\circ C$, for a time ranging from about 2 to about 8 hours. The reaction of the compounds of formula (XXV) with
- 25

The compounds of formula (IX) wherein Z is CH₂, R₆ is -CONH₂ in position 3 of the 2-pyrrolidinone system and R₇ is hydrogen, as per formula (XXVIII) below wherein R₁, R₂, R₄, R₅ and m are as above defined



- 5 can be prepared by a process comprising reacting the compounds of formula (VII) with 1,1-cyclopropanedicarboxylic acid or with 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione, thus obtaining the compounds of formula (XXIX)

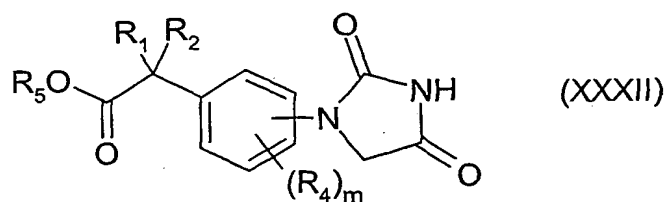


- and by reacting them with ammonia in the presence of an alkylchloroformate or with 1-hydroxybenzotriazole ammonium salt in the presence of a carbodiimide.

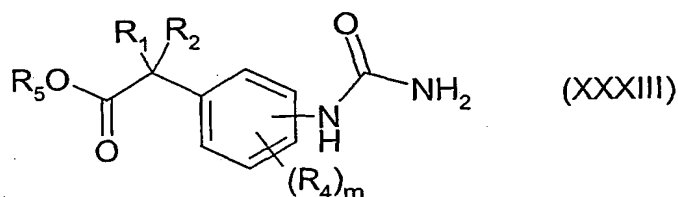
- 10 The reaction of the compounds of formula (VII) with 1,1-cyclopropanedicarboxylic acid to yield the compounds of formula (XXIX) can be carried out in water or in water-ethanol, water-tetrahydrofuran or water-acetonitrile admixtures, at a temperature ranging from about 40°C to about 80°C. Alternatively, the same reaction can be carried
- 15 out with 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione in a suitable solvent such as toluene or xylene at refluxing temperature.

- The reaction of the compounds of formula (XXIX) with ammonia can be carried out in the presence of an alkylchloroformate as a condensing agent, for instance ethylchloroformate, in a suitable solvent such as dichloromethane, chloroform,
- 20 acetonitrile, tetrahydrofuran, 1,4-dioxane or N,N-dimethylformamide, at a temperature ranging from about -10°C to room temperature.

- Alternatively this same reaction can be carried out with 1-hydroxybenzotriazole ammonium salt in the presence of a carbodiimide as a condensing agent, for instance 1,3-dicyclohexylcarbodiimide, 1,3-diisopropylcarbodiimide or 1-(3-
- 25 dimethylaminopropyl)-3-ethylcarbodiimide, in a suitable solvent such as



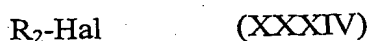
can be prepared by a process comprising reacting the compounds of formula (VII) with potassium cyanate, thus obtaining the compounds of formula (XXXIII)



- 5 and by reacting the compounds of formula (XXXIII) with ethyl 2-chloroacetate.
- The reaction with potassium cyanate can be carried out in a suitable solvent such as acetonitrile, tetrahydrofuran, 1,4-dioxane or N,N-dimethylformamide, at a temperature ranging from room temperature to about 70°C.
- The subsequent reaction of the compounds of formula (XXXIII) with ethyl 2-chloroacetate can be carried out in the presence of a base such as sodium or potassium
- 10 hydroxide in a suitable solvent such as N,N-dimethylformamide, tetrahydrofuran or diethylether, at a temperature ranging from room temperature to about 60°C.

The compounds of formula (VIII) wherein one of R₁ or R₂ is hydrogen and the other is

15 alkyl (e.g. R₁ as hydrogen and R₂ as alkyl), and R₃, R₄, R₅ and m are as described above, can be prepared by reacting the compounds of formula (VIII) wherein R₁ and R₂ are both hydrogen atoms, with the compounds of formula (XXXIV) below



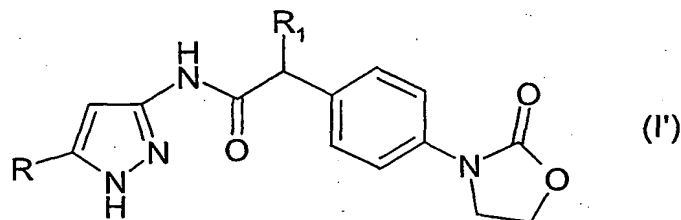
wherein R₂ is alkyl and Hal is a halogen atom, by working in the presence of a base

20 such as potassium tert-butoxide or sodium hydroxide, in a suitable solvent such as tetrahydrofuran, 1,4-dioxane or N,N-dimethylformamide, at a temperature ranging from about -70°C to room temperature.

The compounds of formula (VIII) wherein one of R₁ or R₂ is hydrogen or fluorine and

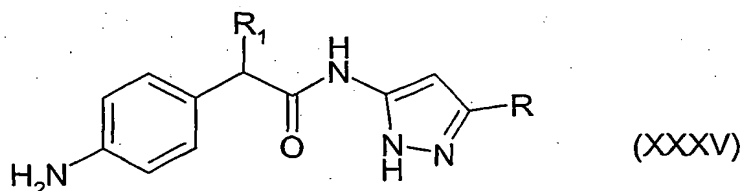
25 the other is fluorine, and R₃, R₄, R₅ and m are as described above, can be prepared by

In addition to the above, herewith provided is also a novel process for preparing the compounds of the invention of formula (I')

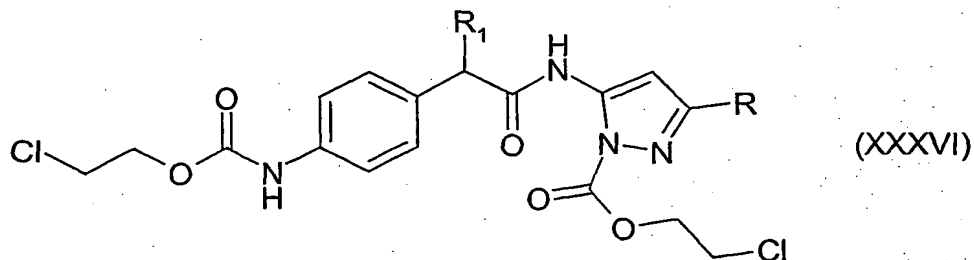


wherein R is a C₃-C₅ cycloalkyl group, R₁ is a hydrogen atom or a methyl group, and the pharmaceutically acceptable salts thereof; which process comprises:

a) reacting the compounds of formula (XXXV)



wherein R and R₁ are as described above, with chloroethylchloroformate in the presence of a base such as pyridine, triethylamine or N,N-diisopropylethylamine and in a suitable solvent such as pyridine, dichloromethane, tetrahydrofuran or N,N'-dimethylformamide, at a temperature ranging from about -20°C to room temperature, thus obtaining the compounds of formula (XXXVI)



wherein R and R₁ are as described above;

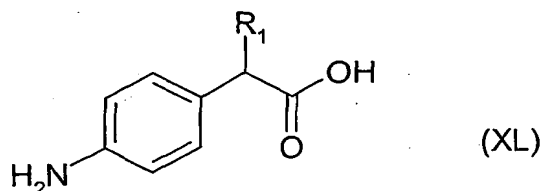
b) reacting the compounds of formula (XXXVI) with a suitable base such as potassium carbonate or 1,8-diazabicyclo[5.4.0]undec-7-ene in a suitable solvent such as N,N-dimethylformamide or N,N-dimethylacetamide, at a temperature ranging from room temperature to reflux, thus obtaining the compounds of formula (XXXVII)

The hydrolysis of the compounds of formula (XXXIX) to afford the compounds of formula (XXXV) can be carried out in a suitable solvent such as dichloromethane or ethanol with a suitable acid such as trifluoroacetic, formic or sulphuric acid at room temperature.

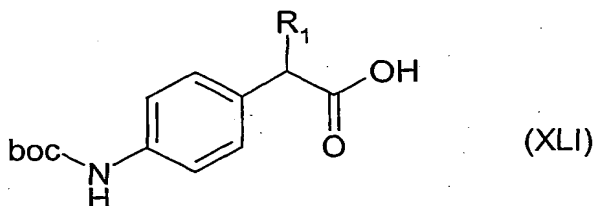
5

The compounds of formula (XXXVIII) can be prepared by a process comprising:

a) reacting the compound of formula (XL) wherein R_1 is as above described



with tert-butoxycarbonylanhydride, thus obtaining the compounds of formula (XLI)



10

b) and by reacting the compounds of formula (XLI) with oxalyl or thionyl chloride.

The reaction between the compounds of formula (XL) with tertbutoxycarbonylanhydride can be carried out in a suitable solvent such as water/1,4-dioxane or water/dichloromethane admixtures, in the presence of a base such as sodium carbonate or sodium hydroxide, at a temperature ranging from about 0°C to room temperature.

15

The reaction between the compounds of formula (XLI) with oxalyl or thionyl chloride can be carried out in a suitable solvent such as dichloromethane, tetrahydrofuran or ethyl acetate, in the presence of a catalytic amount of dimethylformamide at a temperature ranging from about 0°C to reflux.

20

As it will be readily appreciated, if the compounds of formula (I) also comprising those of formula (I'), prepared according to the processes described above, are obtained as an admixture of isomers, their separation into the single isomers of formula (I), or of

25

The inhibition assay of cdk2/Cyclin A activity was performed according to the following protocol

Kinase reaction: 1.5 μ M histone H1 substrate, 25 μ M ATP (0.5 uCi P33g-ATP), 100 ng
5 Cyclin A/cdk2 complex, 10 μ M inhibitor in a final volume of 100 μ l buffer (TRIS HCl
10 mM pH 7.5, MgCl₂ 10 mM, 7.5 mM DTT) were added to each well of a 96 U
bottom well plate. After 10 min at 37°C incubation, reaction was stopped by 20 μ l
EDTA 120 mM.

10 Capture: 100 μ l were transferred from each well MultiScreen plate, to allow substrate
binding phosphocellulose filter. Plates were then washed 3 times with 150 μ l/well
PBS Ca⁺⁺/Mg⁺⁺ free and filtered by MultiScreen filtration system..

15 Detections: filters were allowed to dry at 37°C, then 100 μ l/well scintillant were
added and 33P labelled histone H1 was detected by radioactivity counting in the Top-
Count instrument.

Results: data were analyzed and expressed as % inhibition referred to total activity of
enzyme (=100%).

20 All compounds showing inhibition > 50 % were further analyzed in order to study and
define the kinetic-profile of the inhibitor via K_i calculation.

The protocol used was the same described above, except for ATP and substrate
concentrations. Either the concentrate of ATP and histone H1 substrate were varied: 4,
25 8, 12, 24, 48 μ M for ATP (containing proportionally diluted P33g-ATP) and 0.4, 0.8,
1.2, 2.4, 4.8 μ M for histone were used in absence and presence of two different,
properly chosen inhibitor concentrations.

Experimental data were analyzed by the computer program "SigmaPlot" for K_i
determination, using a random bireactant system equation:

IC50 values were calculated using a variation of the four parameter logistics equation:

$$Y = 100/[1 + 10^{\{(LogEC50 - X)*Slope\}}]$$

5 Where X = log(uM) and Y = % Inhibition.

Given the above inhibition assays, the compounds of formula (I) of the invention resulted to possess a remarkable cdk inhibitory activity. These compounds are thus useful in therapy against proliferative disorders caused by and/or associated with an
10 altered cell cycle dependent kinase activity.

In particular, when tested against cdk2/A, a representative compound of the invention, namely (2S)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide, resulted to possess an inhibitory activity, expressed as IC₅₀, of 8 nM.

15

By restricting the unregulated proliferation of tumor cells, the compounds of formula (I) are therefore useful in therapy in the treatment of various tumors such as, for instance, carcinomas, e.g., mammary carcinoma, carcinoma, bladder carcinoma, colon carcinoma, ovary endometrial tumors, sarcomas, e.g., soft tissue and bone sarcomas,
20 and the hematological malignancies such as, e.g., leukemias.

In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis a restenosis, and in the treatment of Alzheimer's disease.

25

The compounds of the present invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents,
30 immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), matrixmetalloprotease inhibitors, telomerase inhibitors, tyrosine kinase

The pharmaceutical compositions containing the compounds of the invention are usually prepared following convention methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound,
5 diluents, e.g., lactose, dextrose saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g., silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g., starches, arabic gum, gelatin methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disintegrating agents, e.g., a starch, alginic acid, alginates or sodium starch glycolate; effervescing
10 mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. These pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

15 The liquid dispersions for oral administration may be, e.g., syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum,
20 agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., sterile water, olive oil, ethyl oleate, glycols, e.g., propylene glycol, and, if desired, a suitable amount of
25 lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain as a carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous isotonic saline solutions or they may contain as a carrier propylene glycol,

The suppositories may contain together with the active compound a pharmaceutically
30 acceptable carrier, e.g., cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

70/30 and stirred for 3 hours at 5°C. The solid was filtered through a Buchner funnel and then dried at 40°C under vacuum yielding 2 g (90 %yield) of the title compound.

Following the same method, but employing 3-cyclobutyl- or 3-cyclopentyl-oxopropanenitrile, tertbutyl-5-amino-3-cyclobutyl- or tertbutyl-5-amino-3-cyclopentyl-

5 1H-pyrazole-1-carboxylate can be prepared.

Example 2

2-(4-aminophenyl)propanoic-acid

10 10 g (0.05 mol) of 2-(4-nitrophenyl)propanoic acid were dissolved in a mixture of 5 ml of water and 100 ml of methanol and 0.65 g of Pd/C 5% were added. The mixture was submitted to hydrogenation at 60 psi for 2 hours at room temperature. After the separation of the catalyst by filtration on celite the methanol was evaporated under vacuum and the title compound was crystallised from water on cooling (7 g; 85 % yield).

15 ESI (+) MS: m/z 166 (100, MH⁺);

¹H-NMR (400 MHz, DMSO-d₆) ppm: 7.08-6.71 (2d, 4H, CH-phenyl, J=7.1 Hz), 3.76 (q, 1H, CH-Me, J=7.6 Hz), 1.53 (d, 3H, CH₃, 7.6 Hz)

Example 3

(2S)-2-(4-aminophenyl)propanoic acid and (2R)-2-(4-aminophenyl)propanoic acid

20 To 4.34 g of 2-(4-aminophenyl)propanoic acid, 26 ml of water and 3.94 g of L-(+)-tartaric acid were added. The mixture was heated at 80°C under stirring until complete solution. Heating was then stopped and the solution made to spontaneously cool. After 24 hours 3.8 g of levorotatory tartrate were filtered and dried. The solution containing
25 the dextrorotatory tartrate was concentrated under vacuum at 40°C to evaporate about 10 ml of water. The solution was then cooled at 30°C and 1.047 g of sodium hydrate were added. The (+)-(2S)-2-(4-aminophenyl)propanoic acid was collected by filtration and dried to give 1.36 g ($\alpha_D^{20} = +73.0^\circ$; C=0.1 % in methanol). Treating the levorotatory tartrate with sodium hydrate the (-)-(2R)-2-(4-aminophenyl)propanoic
30 acid was obtained.

¹H-NMR (400 MHz, DMSO-d₆) ppm: 7.08-7.35 (2d, 4H, CH-phenyl, J=8.6 Hz), 3.76 (q, 1H, CH-Me, J=7.6 Hz), 3.80 (m, 2H, CH₂N), 4.45 (m, 2H, CH₂O), 1.53 (d, 3H, CH₃, 7.6 Hz)

Analogously, the following intermediates can be prepared starting from the suitable
5 chloro derivatives:

(2R)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanoic acid;

(2S)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanoic acid;

4-(2-oxo-1,3-oxazolidin-3-yl)phenylacetic acid;

ESI (+) MS: m/z 222 (100, MH⁺);

10 ¹H-NMR (400 MHz, DMSO-d₆) ppm: 7.10-7.38 (2d, 4H, CH-phenyl, J=8.7 Hz), 3.43 (s, 2H, CH₂Ph), 3.79 (m, 2H, CH₂N), 4.45 (m, 2H, CH₂O).

Example 6

N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide

15 3.36 g (14.3 mmol) of 2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanoic acid were suspended in 100 ml of dichloromethane. The mixture was cooled to 0°C and 1.63 ml (18.67 mmol) of oxalyl chloride and 0.5 ml of N,N-dimethylformamide were added. After 3 hours at room temperature the solvent was evaporated. The resulting acyl
20 chloride, without any further purification, was dissolved in 100 ml of tetrahydrofuran and added dropwise to a solution of 2.87 g (12.87 mmol) of tert-butyl-5-amino-3-cyclopropyl-1H-pyrazole-1-carboxylate and 16 ml (85.8 mmol) of N,N-diisopropylethylamine in 80 ml of tetrahydrofuran at 0°C. After 8 hours at room temperature, the solvent was evaporated, the residue redissolved in dichloromethane
25 and washed with a saturated solution of sodium hydrogenocarbonate. The organic layer was dried over sodium sulphate and evaporated under vacuum. The resulting protected amide, without any further purification, was redissolved in 18 ml of dichloromethane and 2 ml of trifluoroacetic acid were added. After 3 hours at room temperature, the solvent was evaporated, the residue taken up with dichloromethane and washed with a
30 sodium hydrogenocarbonate solution. The organic layer was dried over sodium sulfate

N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;

(2R)-N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;

5 (2S)-N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;

N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]acetamide.

Example 7

10 2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoic acid

12 g (73 mmol) of 2-(4-aminophenyl)propanoic acid were suspended in 140 mL of 1,4-dioxane and 140 ml of water and treated with 7.6 g (72 mmol) of sodium carbonate dissolved in 72 mL of water.

The resulting solution, cooled to 4°C, was treated with 17.2 g (79 mmol) of tert-butoxycarbonyl anhydride and stirred over night allowing the temperature to reach
15 room temperature. The solvent was evaporated, the aqueous phase was washed with ethylacetate, diluted with the same solvent and treated under stirring with 1M potassium hydrogensulphate. The organic layer was separated and extracted with ethylacetate. The combined organic extracts were washed with brine, dried over
20 sodium sulphate and evaporated. 18.18 g (94 % yield) of the title compound were obtained after trituration with hexane.

ESI (+) MS: m/z 266 (100, MH+);

¹H-NMR (400 MHz, DMSO-d₆) ppm: 7.47-7.52 (m, 4H, CH-phenyl), 3.76 (q, 1H, CHMe, J=7.6 Hz), 1.53 (d, 3H, CH₃, J=7.6), 1.51 (s, 9H, tertbutyl).

25 Analogously, the following compounds can be prepared starting from the suitable carboxylic acid:

(2R)-2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoic acid;

(2S)-2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoic acid;

2-{4-[(tert-butoxycarbonyl)amino]phenyl}acetic acid;

30 ESI (+) MS: m/z 252 (100, MH+);

tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}acetyl)amino]-3-cyclopropyl-1H-pyrazole-1-carboxylate.

Analogously, but using tert-butyl-5-amino-3-cyclobutyl-1H-pyrazole-1-carboxylate the following compounds can be prepared starting from the suitable carboxylic acid:

5 tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoyl)amino]-3-cyclobutyl-1H-pyrazole-1-carboxylate;

(2R)-tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoyl)amino]-3-cyclobutyl-1H-pyrazole-1-carboxylate;

(2S)-tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoyl)amino]-3-cyclobutyl-1H-pyrazole-1-carboxylate;

tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}acetyl)amino]-3-cyclobutyl-1H-pyrazole-1-carboxylate.

Analogously, but using tert-butyl-5-amino-3-cyclopentyl-1H-pyrazole-1-carboxylate the following compounds can be prepared starting from the suitable carboxylic acid:

15 tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoyl)amino]-3-cyclopentyl-1H-pyrazole-1-carboxylate;

(2R)-tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoyl)amino]-3-cyclopentyl-1H-pyrazole-1-carboxylate;

(2S)-tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoyl)amino]-3-cyclopentyl-1H-pyrazole-1-carboxylate;

tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}acetyl)amino]-3-cyclopentyl-1H-pyrazole-1-carboxylate.

Example 9

25 2-(4-aminophenyl)-N-(5-cyclopropyl-1H-pyrazol-3-yl)propanamide

11.8 g (25.26 mmol) of tert-butyl 5-[(2-{4-[(tert-butoxycarbonyl)amino]phenyl}propanoyl)amino]-3-cyclopropyl-1H-pyrazole-1-

carboxylate were dissolved in 200 ml of dichloromethane and 30 ml of trifluoroacetic acid were added. After 2.5 hours at room temperature the solvent was evaporated and

30 the residue taken up with dichloromethane and washed with a saturated solution of

Example 10

2-chloroethyl 5-{{2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)propanoyl}amino}-3-cyclopropyl-1H-pyrazole-1-carboxylate

154 mg (0.57 mmol) of 2-(4-aminophenyl)-N-(5-cyclopropyl-1H-pyrazol-3-yl)propanamide were dissolved in 1.9 ml of dry pyridine at 4°C under argon atmosphere and 0.12 ml (1.148 mmol) of 2-chloroethylchloroformate were added dropwise. After 2.5 hours the reaction mixture was poured into ice and the precipitate solid collected by filtration, affording 225 mg (82 % yield) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) ppm: 7.37-7.41 (m, 4H, CH-phenyl), 3.32 (s, 1H, CH-pyrazole), 3.85 (q, 1H, CHMe, J=6.8 Hz), 1.24 (d, 3H, CH₃, J=6.8 Hz), 1.93 (m, 1H, CH-cyclopropyl), 1.27-1.35 (2d, 4H, CH₂-cyclopropyl), 3.63-3.85 (m, 4H, CH₂O), 4.30 (m, 4H, CH₂Cl).

Analogously, but employing the suitable amide derivatives, the following compounds can be prepared:

2-chloroethyl 5-[[{(2R)-2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)propanoyl}amino]-3-cyclopropyl-1H-pyrazole-1-carboxylate;

2-chloroethyl 5-[[{(2S)-2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)propanoyl}amino]-3-cyclopropyl-1H-pyrazole-1-carboxylate;

2-chloroethyl 5-{{2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)acetyl}amino}-3-cyclopropyl-1H-pyrazole-1-carboxylate;

2-chloroethyl 5-[[{(2R)-2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)propanoyl}amino]-3-cyclobutyl-1H-pyrazole-1-carboxylate;

2-chloroethyl 5-[[{(2S)-2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)propanoyl}amino]-3-cyclobutyl-1H-pyrazole-1-carboxylate;

2-chloroethyl 5-{{2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)propanoyl}amino}-3-cyclobutyl-1H-pyrazole-1-carboxylate;

2-chloroethyl 5-{{2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)acetyl}amino}-3-cyclobutyl-1H-pyrazole-1-carboxylate;

2-chloroethyl 5-[[{(2R)-2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)propanoyl}amino]-3-cyclopentyl-1H-pyrazole-1-carboxylate;

2-chloroethyl 5-[[{(2S)-2-(4-{{(2-chloroethoxy)carbonyl}amino}phenyl)propanoyl}amino]-3-cyclopentyl-1H-pyrazole-1-carboxylate;

N-(3-cyclobutyl-1H-pyrazol-5-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide

N-(3-cyclobutyl-1H-pyrazol-5-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]acetamide;

N-(3-cyclopentyl-1H-pyrazol-5-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide

(2R)-N-(3-cyclopentyl-1H-pyrazol-5-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;

(2S)-N-(3-cyclopentyl-1H-pyrazol-5-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;

N-(3-cyclopentyl-1H-pyrazol-5-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]acetamide.

Example 12

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide

1.29 g (5.56 mmol) of 2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanoic acid were dissolved in 20 ml of dichloromethane and 0.95 ml (5.56 mmol) of N,N-diisopropylethylamine and 1.06 g (5.56 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide were added under stirring at 0°C. After 20 minutes at the same temperature 0.62 g (2.78 mmol) of tertbutyl-5-amino-3-cyclopropyl-1H-pyrazole-1-carboxylate dissolved in 10 ml of dichloromethane were added dropwise. After 12 hours at room temperature, the solution was washed with a sodium hydrogenocarbonate saturated solution, dried over anhydrous sodium sulphate and concentrated in vacuo to give 0.85 g (70 % yield) of tertbutyl-3-cyclopropyl-5-({2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanoyl}amino)-1H-pyrazole-1-carboxylate. Without

any further purification this intermediate was redissolved in 40 ml of ethanol and 2 ml of 10 % sulphuric acid were added. After 12 hours at room temperature under stirring the solution was neutralized with sodium hydrogenocarbonate, the ethanol evaporated and the resulting precipitate collected, washed with water and dessiccated in vacuo to give 590 mg of the title compound (90 % yield).

By working in an analogous way and by using the suitable carboxylic acid, the following compounds can be prepared:

- 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-2-oxoethyl}phenyl)-5-oxo-3-pyrrolidinecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl]propanamide;
- 5 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-1-pyrrolidinyl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(6-methoxy-1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-oxo-1H-benzo[de]isoquinolin-2(3H)-yl)phenyl]propanamide;
- 10 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1H-pyrrol-1-yl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxo-1-imidazolidinyl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-imidazolidinyl)phenyl]propanamide;
- 15 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)phenyl]propanamide;
- 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-2-oxoethyl}phenyl)-5-hydroxy-1H-pyrazole-3-carboxamide;
- 20 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-oxo-1-pyrazolidinyl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-1-pyrazolidinyl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)phenyl]propanamide;
- 25 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-4-morpholinyl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-piperidinyl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-piperazinyl)phenyl]propanamide;
- 30 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(4-morpholinyl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-pyrrolidinyl)phenyl]propanamide;

- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(4-hydroxy-2-oxo-1-pyrrolidinyl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-hydroxy-4,4-dimethyl-2-oxo-1-pyrrolidinyl)phenyl]acetamide;
- 5 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-2-oxo-3-pyrrolidinecarboxamide;
- 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-5-oxo-3-pyrrolidinecarboxamide;
- 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-5-oxo-2-
- 10 pyrrolidinecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-1-pyrrolidinyl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxotetrahydro-1(2H)-pyrimidinyl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-1,2,4-triazolidin-4-
- 15 yl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-1-imidazolidinyl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxo-1-imidazolidinyl)phenyl]acetamide;
- 20 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-imidazolidinyl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)phenyl]acetamide;
- 25 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-5-hydroxy-1H-pyrazole-3-carboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-oxo-1-pyrazolidinyl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-1-pyrazolidinyl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxo-3,4-dihydro-1(2H)-
- 30 pyrimidinyl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-4-morpholinyl)phenyl]acetamide;

[4-(2-oxo-3,3a,6,6a-tetrahydrocyclopenta[b]pyrrol-1(2H)-yl)phenyl]acetic acid;

[4-(2-oxo-5-phenyl-1-pyrrolidinyl)phenyl]acetic acid;

{4-[2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]phenyl}acetic acid;

[4-(3-hydroxy-2-oxo-1-pyrrolidinyl)phenyl]acetic acid;

5 [4-(3-hydroxy-4,4-dimethyl-2-oxo-1-pyrrolidinyl)phenyl]acetic acid;

[4-(4-hydroxy-2-oxo-1-pyrrolidinyl)phenyl]acetic acid;

{4-[2-(aminocarbonyl)-5-oxo-1-pyrrolidinyl]phenyl}acetic acid

Example 14

10 Methyl 2-(4-aminophenyl)propanoate

10 g (0.06 mol) of 2-(4-aminophenyl)propanoic acid were dissolved in 100 ml of methanol and 6.5 ml of 96 % sulphuric acid were added dropwise at 0°C. After 6 hours the methanol was evaporated and the residue poured into icy water. The solution was then basified with 30 % ammonium hydrate and extracted with dichloromethane, giving, after treatment with anhydrous sodium sulfate and concentration under vacuum, 15 9.6 g (90 %yield) of the title compound.

By working in an analogous way and by employing 2-(4-aminophenyl)acetic acid, methyl 2-(4-aminophenyl)acetate can be prepared.

Example 15

20 Methyl 2-[4-(1-pyrrolidinyl)phenyl]propanoate

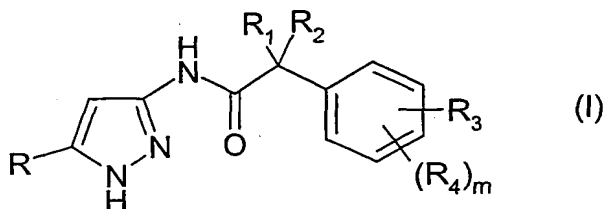
17.9 g (0.1 mol) of methyl 2-(4-aminophenyl)propanoate were dissolved in 450 ml of N,N-dimethylformamide and 15.3 (0.13 mol) of 1,4-dibromobutane and 69.6 ml (0.4 mol) of N,N-diisopropylethylamine were added. The mixture was heated under stirring at 90°C for 5 hours. The solvent was then evaporated under vacuum, the residue redissolved in dichloromethane and the resulting solution washed with water, dried over anhydrous sodium sulphate and concentrated. The crude was finally purified on a Florisil (200-300 mesh) column by using n-hexane as eluant, leading 14 g (60 % yield) of the title compound.

By working in an analogous way and by employing the suitable carboxylic acid, the following compounds can be prepared:

- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide;
- 5 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(6-methoxy-1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl]propanamide;
- 10 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-oxo-1H-benzo[de]isoquinolin-2(3H)-yl)phenyl]propanamide;
- 15 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1H-pyrrol-1-yl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)phenyl]propanamide;
- 2-[2-chloro-4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]-N-(5-cyclopropyl-1H-pyrazol-3-yl)propanamide;
- 20 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-hydroxy-3-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-oxooctahydro-2H-isoindol-2-yl)phenyl]acetamide;
- 25 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl]acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(6-methoxy-1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide;
- 30 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)phenyl]acetamide;

CLAIMS:

1) A method for treating cell proliferative disorders associated with an altered cell cycle dependent kinase activity, by administering to a mammal in need thereof an effective amount of a phenylacetamido-pyrazole derivative represented by formula (I):



wherein

R is an optionally substituted C₃-C₅ cycloalkyl group;

R₁ and R₂, the same or different, represent hydrogen, halogen, amino, hydroxy or a group selected from straight or branched C₁-C₅ alkyl optionally substituted by amino or hydroxy, straight or branched C₁-C₅ perfluorinated alkyl or straight or branched C₁-C₅ alkoxy or, taken together with the carbon atom to which they are bonded, R₁ and R₂ form an exomethylene (>C=CH₂) group or a C₃-C₄ cycloalkyl group;

R₃, in position 3 or 4 of the phenyl ring, is a group of formula



representing a 5 or 6 membered saturated or unsaturated nitrogen containing heterocycle; optionally containing from 1 to 2 additional heteroatoms, the same or different, selected from nitrogen, oxygen or sulfur; optionally substituted in any of the free positions by one or more groups selected from halogen; hydroxy; aminocarbonyl; C₁-C₄ alkylaminocarbonyl; oxo groups (>C=O, >S=O, >SO₂); exomethylene (>C=CH₂); straight or branched C₁-C₄ alkyl, perfluorinated alkyl, hydroxyalkyl or alkoxy groups; C₂-C₄ alkenyl or aryl groups; optionally condensed with carbocyclic or heterocyclic rings, either saturated or unsaturated, either monocyclic or bicyclic, each of which being optionally further substituted as above defined;

m is 0 or an integer from 1 to 4;

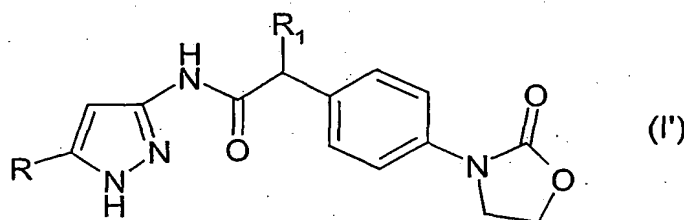
if present, each R₄ is, the same or different, halogen, hydroxy or a group selected from straight or branched C₁-C₄ alkyl, perfluorinated alkyl or alkoxy;

6) The method according to claim 1 which provides treatment or prevention of radiotherapy-induced or chemotherapy-induced alopecia.

7) The method according to claim 1 further comprising subjecting the mammal in need thereof to a radiation therapy or chemotherapy regimen in combination with at least one cytostatic or cytotoxic agent.

8) The method according to claim 1 wherein the mammal in need thereof is a human.

9) The method according to claim 1 which comprises administering to a mammal in need thereof an effective amount of a phenylacetamido-pyrazole derivative represented by formula (I):



wherein R is a C₃-C₅ cycloalkyl group, R₁ is a hydrogen atom or a methyl group; or a pharmaceutically acceptable salt thereof.

10) The method according to claim 9 wherein the compound of formula (I) is (2S)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide.

11) A method for inhibiting cyclin dependent kinase activity which comprises contacting the said kinase with an effective amount of a compound of formula (I) as defined in claim 1.

12) A phenylacetamido-pyrazole derivative represented by formula (I):

- b) when R is cyclopropyl, one of R₁ and R₂ is a hydrogen atom and the other is methyl, ethyl, n-propyl or n-butyl, then the nitrogen-containing heterocycle of formula (II) is other than 1,3-dihydro-2H-isoindol-2-yl or 1-oxo-1,3-dihydro-2H-isoindol-2-yl.

5

13) A phenylacetamido-pyrazole derivative of formula (I), according to claim 12, wherein R is a C₃-C₅ cycloalkyl group; one of R₁ and R₂ is hydrogen and the other is a halogen atom or a straight or branched C₁-C₄ alkyl, perfluorinated alkyl or aminoalkyl group; and R₃, R₄ and m have the meanings reported in claim 12.

10

14) A phenylacetamido-pyrazole derivative of formula (I), according to claim 12, wherein R is a C₃-C₅ cycloalkyl group; R₁ and R₂ are both halogen atoms or taken together with the carbon atom to which they are bonded form an exomethylene group or a C₃-C₄ cycloalkyl group; and R₃, R₄ and m have the meanings reported in claim 12.

15

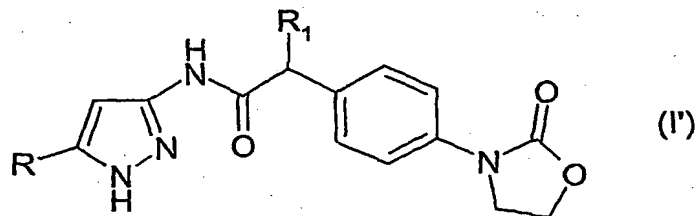
15) A phenylacetamido-pyrazole derivative of formula (I), according to claim 12 wherein R₁ and R₂ are both fluorine atoms, and R₃, R₄ and m have the meanings reported in claim 12.

20

16) A phenylacetamido-pyrazole derivative of formula (I), according to claim 12, wherein R, R₁, R₂, R₄ and m are as defined in claim 12 and R₃, being optionally further substituted and/or condensed, is selected from the group consisting of:

isoindol-2-yl; 2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl; 2,5-dioxo-1-pyrrolidinyl; 2,5-dioxo-1-pyrrolidinyl; 6-methoxy-1-oxo-1,3-dihydro-2H-isoindol-2-yl; 1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl; 1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl; 1-oxo-1H-benzo[de]isoquinolin-2(3H)-yl; 1H-pyrrol-1-yl; 7-hydroxy-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl; 3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl; 1-oxo-1,3-dihydro-2H-isoindol-2-yl; 2,4-dioxotetrahydro-1(2H)-pyrimidinyl; 3,5-dioxo-1,2,4-triazolidin-4-yl; 2,5-dioxo-1-imidazolidinyl; 2,4-dioxo-1-imidazolidinyl; 2-oxo-1-imidazolidinyl; 2-oxo-2,3-dihydro-1H-imidazol-1-yl; 2-oxo-2,3-dihydro-1H-imidazol-1-yl; 5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl; 5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl; 5-hydroxy-1H-pyrazole-3-carboxamide; 3-oxo-1-pyrazolidinyl; 3,5-dioxo-1-pyrazolidinyl; 2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl; 3,5-dioxo-4-morpholinyl; 2-oxo-1-piperidinyl; 1-piperazinyl; 4-morpholinyl and 1-piperidinyl.

18) A phenylacetamido-pyrazole derivative of formula (I), according to claim 12,
which is represented by formula (I')



wherein

R is a C₃-C₅ cycloalkyl group;

R₁ is a hydrogen atom or a methyl group;

and the pharmaceutically acceptable salts thereof.

19) A phenylacetamido-pyrazole derivative of formula (I'), according to claim 18,
wherein R is cyclopropyl.

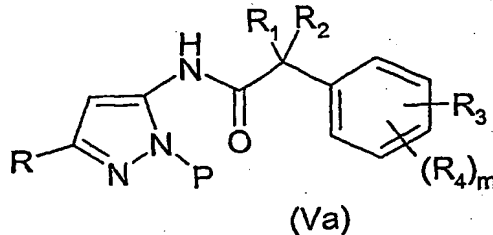
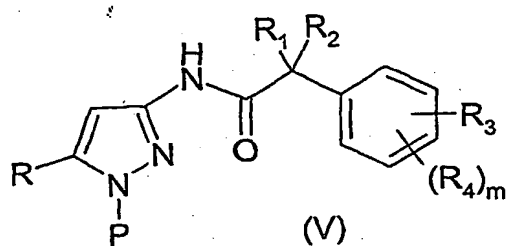
20) A phenylacetamido-pyrazole derivative of formula (I'), according to claim 18,
wherein R₁ is methyl.

11. (2S)-N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]propanamide;
12. N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]acetamide.
- 5 13. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
14. (2S)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
15. (2R)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
- 10 16. N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
17. (2S)-N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
- 15 18. (2R)-N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
19. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-fluoro-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]acetamide;
- 20 20. 2-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]acetamide;
21. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,2-difluoro-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]acetamide;
22. N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,3,3-trifluoro-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
- 25 23. 3-amino-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-pyrrolidinyl)phenyl]propanamide;
24. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-methyl-2-oxo-1-pyrrolidinyl)phenyl]acetamide;
25. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-methyl-2-oxo-1-pyrrolidinyl)phenyl]propanamide;
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41. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-hydroxy-4,4-dimethyl-2-oxo-1-pyrrolidinyl)phenyl]propanamide;
42. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-2-oxo-3-pyrrolidinecarboxamide;
- 5 43. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-2-oxoethyl}phenyl)-2-oxo-3-pyrrolidinecarboxamide;
44. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-5-oxo-3-pyrrolidinecarboxamide;
45. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-2-oxoethyl}phenyl)-5-oxo-3-pyrrolidinecarboxamide;
- 10 46. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-5-oxo-2-pyrrolidinecarboxamide;
47. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-2-oxoethyl}phenyl)-5-oxo-2-pyrrolidinecarboxamide;
- 15 48. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]acetamide;
49. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide;
50. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-hydroxy-3-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide;
- 20 51. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-oxooctahydro-2H-isoindol-2-yl)phenyl]acetamide;
52. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(1-oxooctahydro-2H-isoindol-2-yl)phenyl]propanamide;
- 25 53. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl]acetamide;
54. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl]propanamide;
55. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-1-pyrrolidinyl)phenyl]acetamide;
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72. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-1-imidazolidinyl)phenyl]acetamide;
73. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,5-dioxo-1-imidazolidinyl)phenyl]propanamide;
- 5 74. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxo-1-imidazolidinyl)phenyl]acetamide;
75. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2,4-dioxo-1-imidazolidinyl)phenyl]propanamide;
76. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-imidazolidinyl)phenyl]acetamide;
- 10 77. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-1-imidazolidinyl)phenyl]propanamide;
78. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)phenyl]acetamide;
- 15 79. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)phenyl]propanamide;
80. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)phenyl]acetamide;
81. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)phenyl]propanamide;
- 20 82. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-oxoethyl}phenyl)-5-hydroxy-1H-pyrazole-3-carboxamide;
83. 1-(4-{2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-2-oxoethyl}phenyl)-5-hydroxy-1H-pyrazole-3-carboxamide;
- 25 84. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-oxo-1-pyrazolidinyl)phenyl]acetamide;
85. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3-oxo-1-pyrazolidinyl)phenyl]propanamide;
86. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-1-pyrazolidinyl)phenyl]acetamide;
- 30 87. N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-[4-(3,5-dioxo-1-pyrazolidinyl)phenyl]propanamide;

wherein R_1 , R_2 , R_3 , R_4 and m are as defined in claim 12 and R' represents hydroxy or a halogen atom, thus obtaining the compounds of formula (V) or (Va)



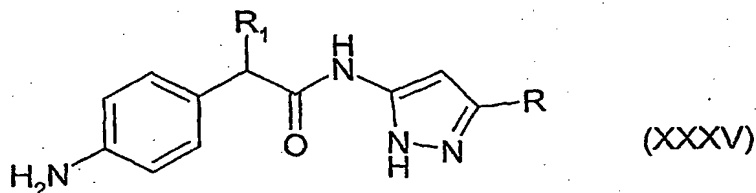
- 5 b) and deprotecting the compounds of formula (V) or (Va) so as to obtain the derivatives of formula (I) and, if desired, converting them into pharmaceutically acceptable salts thereof.

25) The process of claim 24 wherein, within the compounds of formula (III), or
10 (IIIa), P represents the group tert-butoxycarbonyl (boc).

26) The process of claim 24 wherein, within the compounds of formula (IV), R' is hydroxy or a chlorine atom.

15 27) A process for preparing the compounds of formula (I') and the pharmaceutically acceptable salts, as defined in claim 18, which process comprises:

- a) reacting the compounds of formula (XXXV)



wherein R and R_1 are as defined in claim 18, with chloroethylchloroformate in the
20 presence of a base, thus obtaining the compounds of formula (XXXVI)

32) A product or kit comprising a compound of formula (I) or a pharmaceutically acceptable salt as defined in claim 12 or a pharmaceutical composition thereof, as defined in claim 30, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

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33) A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 12, for use as a medicament.

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34) Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 12, in the manufacture of a medicament with cell cycle dependent kinase inhibitory activity.

35) Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 12, in the manufacture of a medicament with antitumor activity.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

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